REMARKS/ARGUMENTS

Status

Claims 67, 69-73 and 75-87 are under examination.

Claim Objections

Claim 70 is amended to correct a typographical error, thus overcoming the objection.

Rejections Under 35 USC 112, second paragraph

Claim 87 is amended to correct a typographical error, thus overcoming the rejection. Applicants thank the Examiner for his careful review of the claims.

Rejections Under 35 USC 102(e)

Claims 67 and 69 were rejected under 35 USC 102(e) in view of US Pat. Pub. 2002/0141903 ("Parunak"). Applicants respectfully traverse.

Parunak differs in a number of respects from the claimed invention. The Office characterizes Parunak on page 4 of the Office Action. Applicants disagree with the Office characterization. In Parunak, a particle-containing fluid is introduced into the enrichment chamber 931. The sample is introduced through input 180 and flowed past open valve 913. Enrichment chamber 931 is bounded by closed valves 919 and 915 and flow-through member 900. Flow through member 900 is a filter (see paragraph [0055]) with "formed of a material having pathways smaller than the diameter of the particles to be enriched, such as pores of less than about 2 microns in diameter" through which fluid can flow. The Office Action asserts that, in addition to fluid components, "smaller particles" can flow though the membrane. However, as discussed below, the reference does not describe or suggest that smaller particles are present, or that if any were present, they would pass though the filter. As a particle-containing fluid is introduced into the enrichment chamber 931, fluid flows out of the enrichment zone through filter 900, while particles (i.e., particles with a diameter larger than the filter pore size) remain trapped in the chamber. The result is that particles are *concentrated* in enrichment chamber. See, e.g., paragraphs [0052] and [0062] of Parunak.

Parunak is directed to using a filter through which fluid passes to concentrate cells in enrichment chamber 931. However, nothing in Parunak suggests separating biological elements from other biological elements. As noted above, contrary to the Office Action, Parunak only teaches a concentration system in which particles are retained while allowing "fluid of the particle-containing fluid" to exit the enrichment zone. See, e.g., paragraph [0009]. Parunak does not teach that "smaller particles" are present or pass through the filter. Moreover, to the extent it might be a likely consequence of the filter properties that particles such as dirt or debris– if any are present in the fluid- that are smaller than the filter pore size will pass through the filter, it is beyond dispute that Parunak does not describe a filtration system in which an individual biological element or a subset of the biological elements is retained by the filter which other biological elements pass through the filter. In short, Parunak describes concentration of particles (e.g., cells) not separation of biological elements from each other. According, Parunak did not anticipate the present invention.

Further, Claim 67 (as previously presented) recites the step of "physically isolating an individual biological element or a subset of the biological elements of the sample within a microfluidic flow channel wherein the isolation step comprises allowing the individual biological element or the subset of the biological elements to flow past a first valve of the microfluidic device, creating a segment within the flow channel by actuating the first valve and a second valve of the microfluidic device, whereby the element or elements are suspended in solution and are prevented from exiting the segment past the first valve or the second valve". In Parunak, the particle-containing fluid flows past valve 913 into a chamber bounded by closed valves and a filter (elements 919, 915 and 900). Parunak does not describe "physically isolating an individual biological element or a subset of the biological elements [by] creating a segment by actuating the first valve and a second valve." In Parunak, operation of the device requires that valves 919 and 915 must be closed when fluid is flowed past valve 913. There is no step in Parunak in which particles are isolated by actuating a first valve and a second valve of the microfluidic device.

Still further, the Office appears to consider trapped particles in chamber 931 in Parunak is "*physically isolating* [particles] within a microfluidic flow channel". Applicants disagree, but for the sake of expediting prosecution will assume, *arguendo*, the Office's interpretation of "physically isolating". However, even in this case, particles are "physically isolated" by the passage of fluid through filter 900, *not* by actuating any valves.

Alternatively, if the Office believes "physically isolating" is accomplished in Parunak be actuating valve 913, this is clearly a different process than actuating two valves as in the instant invention.

Applicants submit that the difference between the present method and Parunak is substantial. In Parunak, particles enriched (or, according to the Office Action, are separated) based on shared properties (i.e., size). Moreover, using the device of Parunak it appears impossible to isolate individual cells. In contrast, in the present method, individual particles or subsets of particles are isolated and analyzed without regard to cell properties, and individual cells can be isolated.

Even further, nothing in Parunak teaches "providing a sample comprising *heterogeneous* biological elements suspended in solution" as is now claimed. As explained above, Parunak is directed to concentration, not to separation of different biological elements from a heterogeneous mixture of biological elements. In addition to the fact that nothing in Parunak teaches such separation from a heterogeneous mixture, there is no apparent method by which the Parunak device could accomplish this.

For these and other reasons, Applicants submit it is clear that claims 67 and 69 as presented were not anticipated by Parunak.

The claims are amended in this response for improved clarity. Although these amendments are not necessary to distinguish the reference, Applicants note that nothing in Parunak describes the claimed invention.

Rejections Under 35 USC 103(a)

As discussed above, Parunak did not describe or suggest the present invention. None of the secondary references remedies the deficiencies of Parunak.

Accordingly, the Office has not established *prima facie* obviousness for any of the claims.

Parunak in combination with Burlage (US 2003/0099928)

Claims 70-73 and 73 were rejected as allegedly obvious in view of Parunak in combination with Burlage. Nothing in Burlage remedies the deficiencies discussed above. Accordingly the references cited by the Office do not render the claims obvious.

(Moreover, Burlage describes labeling cells using nucleic acid probes and separating them using fluorescence-activated cell sorting. The Office Action appears to suggest that FACS-isolated cells obtained according to Burlage could be processed, i.e., concentrated and then lysed, etc., using the device of Parunak. If this is the Office position, Applicants respectfully submit even if there was any motivation to combine the references in this way, the result would not be similar to the present invention. Alternatively, the Office may be asserting that the separation method of Burlage could be carried out on the device of Parunak. See Office Action, page 10 at top. If this is the Office position, Applicants respectfully submit the references, taken together, neither suggest nor enable FACS-based separations on the device of Parunak, nor provide any expectation of success for so doing.)

Parunak in combination with Nelson (US 6,007,690)

Claims 76, 79, 80, 83, 84 and 87 were rejected as allegedly obvious in view of Parunak in combination with Nelson. The deficiencies of Parunak are discussed above and are not remedied by Nelson. For this reason, the claims are not obvious in view of the cited references.

Moreover, Nelson is asserted by the Office to describe introduction of a lysis solution though a cross-flow injector structure. The Office cites Nelson at Col. 16, lines 65-67, Col. 22, lines 36-53, and Figures 5, 12 and 23 for teaching this element. However, Nelson does not describe introduction of a lysis solution though a cross-flow injector structure.

Col. 16, lines 65-67, referring to Figures 5 and 12, described *electrophoretic flowpaths.* See Col. 12, line 66 to Col 13, line 25 (describing Fig. 5) and Col 14., line 43 – 55 (describing Fig. 12). There is no suggestion at all of introducing a lysis solution. Col. 22-23 and Fig 23 describe injecting lysis solution and cells through separate channels, at separate times, into an extraction chamber. However, Nelson did not describe or suggest cross-flow injection, in which two channels intersect, a slug of fluid comprising cells is introduced into a channel portion from one of the two channels, and lysis solution is introduced to the cells via the second intersecting channel, expelling the cells. See the instant application at, e.g., paragraphs 0212-0217 and Fig. 20A-D.

Nelson is asserted by the Office to describe lysis using a rotary mixer. However, Nelson does not describe lysis using a rotary mixer. The Office cites Col. 22, line 67 to Col. 23, line 10 for teaching this element. Although the Office correctly asserts Nelson describes mixing by arranging the supply channels so that the streams of beads, sample, and lysis solution merge, mixing that can be enhanced electrokinetically by judicious control of the applied electric field and by periodically reversing the polarity of the electrodes placed in the inlet and outlet reservoirs, electrokinetically moving the blood-lysis buffer mixture in an oscillatory manner within the SPE chamber and use of aperture-like structures, the Office does not, and cannot, identify any suggestion in Nelson to use a rotary mixer.

Parunak in combination with Unger (US 6,408,878)

Claims 77, 78, 81, 82, 85 and 86 were rejected as allegedly obvious in view of Parunak in combination with Unger. Unger teaches valves comprising deflectable membranes, but does not remedy the deficiencies of the primary reference.

Request for Interview

Applicants believe the claims are in addition for allowance. The undersigned Applicant's Representative will contact the Examiner to arrange for a telephonic interview to address any remaining issues.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-462-5330.

Respectfully submitted,

Randolph Ted Apple
Reg. No. 36, 429

KILPATRICK TOWNSEND and STOCKTON LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 650-462-5330
Fax: 415-576-0300
63853704 v1